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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,054	11/20/2003	Stephen N. Jones	07917-178001 / UMMC 03-14	3347

26161 7590 10/05/2006

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,054	JONES ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *1-22,30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-29 and 32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-36 are pending. New claims 33-36 have been added. Claims 1-22 and 30-31 are withdrawn to a non-elected invention.

Currently amended and newly added claims 23-29 and 32-36 are under consideration.

Claim objections

Applicant's arguments, see page 7 of arguments, filed 7/12/06, with respect to objection of claims 23-29 and 32 for reading on a non-elected invention have been fully considered and are persuasive. Applicants have amended the claim 23 to remove language "or who is at risk of developing". The rejection of claims 23-29 and 32 has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicant's arguments, see pages 8-9 of arguments, filed on 7/12/06, with respect to the rejection of claims 23-29 and 32 under 35 U.S.C. 112 & 1st paragraph for written description requirement have been fully considered and are persuasive. Applicants have amended claim 23 to remove the phrase "or a biologically active fragment or mutant thereof". The rejection of claims 23-29 and 32 has been withdrawn.

Applicant's arguments, see pages 9-14 of arguments, filed on 7/12/06, with respect to the rejection of claims 23-29 and 32, under 35 U.S.C. 112, 1st paragraph for enablement

requirement have been fully considered and are not persuasive. The rejection of claims 23-29 and 32 has been maintained.

Claims 23-29 and 32-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of treating a subject having, a Wnt5a-associated hematopoietic cancer by administering to the subject a cell comprising a nucleic acid molecule that encodes Wnt5a protein, wherein the amount of the nucleic acid sequence molecule delivered is sufficient to generate therapeutically effective amount of Wnt5a. Embodiments limit the subject to a human patient with leukemia, lymphoma, myeloma, acute leukemia, chronic leukemia, Hodgkin's and non-Hodgkin's lymphoma. Embodiments further limit the invention wherein a subject is treated for said cancer by administering a cell removed from the subject, transducing the cell with a nucleic acid molecule encoding Wnt5a gene and optionally a sequence that encodes a detectable marker, culturing the cell and returning the cell to the subject.

The specification discusses that Wnt5a plays a role in B cell proliferation and differentiation, and acts as tumor suppressor of B cell proliferation to suppress hematopoietic malignancies (specification p 2, lines 23-24). The specification describes that hematopoietic cancers are associated with a reduction in Wnt5a gene expression or protein activity including acute myeloid leukemia (AML) (specification p 4, lines 26-30). The specification recites that "The new methods and compositions described herein are based, in part, on studies that have established Wnt5a as a tumor suppressor in B cells of two mammalian species and the present

experiments were conducted in mice and humans and there is no reason to expect that the findings are not applicable to all Wnt5a-expressing cells and animals" (specification p 13 lines 10-25). The specification further contemplates that cells can be obtained from the subject, transduced with Wnt5a or mutants thereof, in vitro, and then the cells per se can be administered to subjects in the context of replacement therapies. Wnt5a gene is linked to a native Wnt5a promoter and/or other regulatory sequences and introduced into a cell, for example, a B cell that has reduced level of Wnt5a that was previously removed from the subject. The cell can be expanded in culture for some time, and when the cell is returned to the subject, the cell expresses normal amount of Wnt5a. The specification contemplates that such methods can be used to treat a disease associated with reduced Wnt5a expression such as a hematopoietic malignancy (specification p 36-37). While the specification contemplates therapeutic levels of Wnt5a protein expression, in vivo, after transferring Wnt5a transduced cells ex vivo into a subject resulting in the treatment of a Wnt5a-associate hematopoietic cancer (specification p 32-37), the specification fails to provide any relevant teachings or specific guidance or working examples with regard to transducing a blood cell ex vivo with wnt5a and/or obtaining any blood cells from a subject, transduce cells ex vivo with wnt5a, reintroduce the cells into the subject wherein therapeutic levels of the transgene are produced resulting in the treatment of a subject with Wnt5a hematopoietic cancer. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for treating cell based Wnt5a associated hematopoietic cancer. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

The claims are directed to methods of treating Wnt5a associated hamatopoietic cancer, in a subject by transdcucing a cell with Wnt5a ex vivo, producing a therapeutic protein in a cell

or hematopoietic tissue and clearly fall into the realm of cell based gene therapy. The specification has contemplated treating Wnt5a associated AML by cell based Wnt5a gene therapy, such that treatment can be achieved by transplantation of the transduced cells to a target tissue in sufficient number to produce therapeutic levels of the Wnt5a protein, but has not provided any specific guidance or working examples that correlate to treatment of any Wnt5a associated hematopoietic cancer, by transducing a blood cell with Wnt5a ex vivo and transferring said cells in subject resulting in treatment of a Wnt5a-associated cancer. Since the instant specification has failed to provide specific guidance or working examples correlating to treatment of any Wnt5a hematopoietic cancer by the claimed method one of skill in the art could not rely on the state of the cell based gene therapy art to treat a Wnt5a-associated hematopoietic cancer. This is because the art of cell based gene therapy is an unpredictable art with respect to multiplying transduced cells in vitro, source of the cell for therapy, immunological issues, levels of expression of a therapeutic protein necessary to provide therapy; the number of transduced cell needed and mode of administration of the therapeutic cell. These issues are discussed by experts in the field of gene therapy, in published reviews at the time of the instant invention. Cage, (Nature, 392: 18-24, 1998) teach that although the hematopoietic field is the most advanced in clinical applications of cell therapy, the number of cells needed to perform the desired function is a limiting variable, and thus the ability to multiply a population of cells may be critical (p 20, 2nd column). The author further noted that difficulties arise as if the cells either cannot self-renew in vitro, as in the heamatopoietic system (p 20, 2nd column). Gage, also describes that although, the use of allogeneic obviates the time and source restrictions inherent in the use of autologous cells, many of the problems associated with the variability and replicative capacity remain (p 21 1st column). In addition, when considering the functional requirements of a cell and the limitations imposed by the source of the cell, it becomes clear

that there is no single universal donor cell that will be useful for all diseases (Cage, p 23 1st column). **Scanlon** (Anticancer Research, 24: 3-7, 2004) reports that gene therapy cell delivery the challenges to make this work successfully in a patient are several: (1) determining optimal transduction of cells with a transgene or product; (2) gene-transformed cells will require a selective growth advantage over defective cells to repopulate the host; (3) DNA repair genes (minimizes mutations in the gene-transformed cells); (4) genomic stability (for optimal gene expression)?; (5) determining cell type for therapy, embryonic, stem cells or activated differentiated cells ?; (6) incorporating a safety mechanism if a problem arises to destroy the gene transformed cells (i. e. a suicide gene) (p 6, 2nd column). **Becker** (Acta Haematol, 114: 188-197, 2005) while reviewing the current status of gene therapy in autologous transplantation notes that one major problem with CD34 selection is that only a small subset of CD34+ cells fulfill the definition of stem cells as for example cells able to self-renew indefinitely and give rise to all types of blood cell lineages and there is no single precise marker for the stem cell (p 189, 1st column). **Becker** also notes that there is difficulty in maintaining stem cell properties, in particular self-renewal and proliferative capability, after ex vivo manipulations required to optimize retroviral-mediated gene transfer (p 189, 2nd column). Engraftment of transduced cells has also been difficult, as the CD34+ cells that have been incubated ex vivo in cytokines lose repopulating ability in the NOD-scid xenograft model as had been shown for syngeneic marrow cells incubated in expansion cytokines (p 189, 2nd column). **Kohn et al,** (J Intern Med, 249(4): 379-90, 2001) noted that inefficient gene transfer to human hemotopoietic stem cells has imposed the major limitation to successful application of gene therapy (p 379, abstract). While progress has been made in recent years for gene transfer in vivo, blood cell based gene therapy in vivo continues to be unpredictable and inefficient as supported by numerous teachings available in the art. **Budak-Alpdogan et al,** (Cancer Gene Therapy, 12: 849-863, 2005) reports

that in the gene therapy trial for X-SCID, purified BM CD34+ cells were transduced by amphotropic retroviral particles containing a MoMLV-based vector encoding γc cDNA under the transcriptional control of LTR and while the patients showed signs of clinical improvement with increased levels and repertoire of immune effector cells, however, vector integration near the LMO-2 site, an oncogene associated with t-ALL, consequently played a role in dysregulated growth of transgene-positive clones and two patients developed T-cell leukemia 30-34 months after transplantation (p 855, 2nd column).

Moreover, the state of the art of Wnt5a cell based hematopoietic gene therapy is unpredictable and undeveloped. The state of the art lack relevant teachings as to what would be the therapeutic Wnt5a recombinant levels produced in the target hematopoietic cancer cells to treat a subject with Wnt5a associated hematopoietic cancer. In addition, neither the specification nor the art of record provide any guidance for removing a cell from a subject of any hematopoietic cell type transducer the cell with Wnt5a gene, culturing the cell and returning the cell into the subject and as to what would be the appropriate cell dose and route of administration to treat Wnt5a associated hematopoietic cancer. Therefore, the skilled artisan would conclude the state of the art of Wnt5a cell based gene therapy is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for treating Wnt5a associated hematopoietic cancer by Wnt5a cell based gene therapy without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the treatment of a Wnt5a associated hematopoietic cancer, the lack of guidance provided by the specification for the treatment of Wnt5a associated hematopoietic cancer, the absence of working examples that correlate to the treatment Wnt5a associated

hematopoietic cancer, the unpredictable state of the art with respect to cell based Wnt5a gene therapy, the undeveloped state of the art pertaining to the treatment of Wnt5a associated hematopoietic cancer, by Wnt5a cell based gene therapy, and the breadth of the claims directed to Wnt5a-associated hematopoietic cancers, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Response to Arguments

Applicants argue that it is axiomatic that what is well known in the art need not be set forth in detail and methods for making viral vectors suitable for expressing Wnt5a in blood cells were well known in the art at the time of filing the application (arguments p 10). Applicants also argue that while Gage notes there are some difficulties associated with cell based gene therapy in general, these issues are not necessarily applicable to the claimed methods and Gage notes that as few as 3.5×10^3 stem cells would be sufficient to fully reconstitute the hematopoietic system, therefore even if expansion in vitro is difficult, large numbers of cells are not necessarily for the methods to be successful, and the ability to multiply a population of the cells is not critical (arguments p 10). Applicants further argue that because Wnt5a is a secreted protein, the cell type that is used is less critical; any blood cell can be used as Wnt5a secreted into the circulation would be expected to contact the malignant cells and exert the therapeutic effect (arguments p 10-11).

In response this is not found persuasive because the applicants have not provided sufficient guidance to overcome the issue of unpredictability of cell based gene therapy. Applicants have not provided specific guidance and/or working examples wherein even a small number of blood cells transduced with a nucleic acid sequence encoding Wnt5a wherein the amount of nucleic acid molecule delivered is sufficient to generate a therapeutically effective amount of Wnt5a. The art of cell based gene therapy is an unpredictable art with respect to

multiplying transduced cells in vitro, source of the cell for therapy, immunological issues, levels of expression of a therapeutic protein necessary to provide therapy, the number of transduced cell needed and mode of administration of the therapeutic cell. In cell based gene therapy enablement what is axiomatic is the unpredictability of producing ex vivo a Wnt5a transduced cell population competent to generate a therapeutically effective amount of the Wnt5a protein product after returning the cells to the subject resulting in the treatment of a Wnt5a associated hematopoietic cancer. Examiner agrees that it is axiomatic that what is well known in the art need not be set forth in detail and methods for making viral vectors suitable for expressing Wnt5a in blood cells were well known in the art at the time of filing the application, however it is not axiomatic that the Wnt5a transduced blood cell ex vivo when the cell is returned to the subject, the cell expresses a statistically normal amount of Wnt5a and such methods can be used to treat a disease associated with reduced Wnt5a expression, e.g., hematopoietic malignancy (specification p 37). What is contested is not the methodology of cell based gene therapy rather the unpredictability of a correlation between of the execution of the methodology and the effect resulting in the treatment of a Wnt5a associated hematopoietic cancer.

Applicants further argue that Cavazzano-Calvo describes successful treatment of human subjects with severe combined immunodeficiency (SCID)-X disease by administering autologous blood cells transduced with a transgene that encodes a missing cytokine receptor and Bai et al describes the use of lentiviral vector for stable transduction and transgene expression of human blood cells with high efficiency (p 12). Applicants also argue that Wnt5a proteins had been successfully expressed in a number of cell types, including the mesodermal stem cell line QCE6 (Brandon et al) and fetal liver hematopoietic stem cells (Austin et al) thus methods for transducing blood cells and expressing exogenous genes as for example Wnt5a were described in the present application and known in the art (p 12). Applicants further argue

that it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation (p 12). Applicants argue that because individuals with normal levels of Wnt5a do not generally have hematological malignancies (example 10 and figure 16), it would be logical to assume that levels of Wnt5a that are present in a normal subject are sufficient to suppress hematological malignancies, therefore, levels approximating normal would be expected to be therapeutic.

In response this is not found persuasive because applicants have not provided specific guidance wherein a Wnt5a protein had been successfully expressed in a number of blood cell types transduced with Wnt5a in vitro and when said cells transferred into the subject suppress a hematological malignancy indicating the levels approximating normal would be expected to be therapeutic. It is logical to assume that the levels of wnt5a that are present in a normal subject are sufficient to suppress hamatologic malignancies, therefore levels approximating normal would be expected to be therapeutic, however, it is unpredictable as to whether the levels of wnt5a produced by a blood cell transduced with wnt5a ex vivo, wherein the amount of wnt5a generated in vivo constitutes a therapeutically effective amount of wnt5a resulting in the treating a subject with a wnt5a hematopoietic cancer. **Larsson et al,** (Oncogene, 24: 5676-5692, 2005) notes that several different signaling pathways, transcription factors and cell cycle regulators will have to be simultaneously stimulated to achieve efficient expansion of stem cells including wnt siganling (p 5688, figure 6). **Larsson et al,** also notes that regulation of hematopoietic stem and progenitor cells is more complicated in bone marrow microenvironment in vivo than is seen in liquid cultures ex vivo and smad signaling regulates hematopoiesis by cross talk with other regulatory signals and future research will define in more detail how the various pathways interact and how the knowledge obtained can be used to develop advanced cell therapies (abstract). Applicants failed to provide guidance to overcome the limitations of the art and the

unpredictability for practicing claimed invention and as enablement requires the specification to teach how to make and use the claimed invention, as such, the rejection of claims 23-29 and 32 35 is maintained.

Conclusion

No claim is allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram

R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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